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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/653,114	05/24/96	FALCK-PEDERSEN E	19603/233(CR

EXAMINER	
SCHNIZER,R	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/653,114	FALCK-PEDERSEN, ERIK S	
	Examiner	Art Unit	
	Richard Schnizer	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,9 and 17-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,9 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☒ Interview Summary (PTO-413) Paper No(s). *37* .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

The request filed on 5/23/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/653,114 is acceptable and a CPA has been established. A final rejection was mailed on 9/8/00 as Paper No. 35. That action is withdrawn, in view of Applicant's proof of submission of a preliminary amendment on 5/30/00, in favor of the following office action.

In response to the preliminary amendment, claims 2, 7, 8, 10, 11, and 13-15 were canceled, and new claims 18-20 were added. Claims 1, 3, 4, 9, and 17-20 are pending and under consideration.

Rejections Withdrawn

The rejection of claims 1, 3, and 4 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicant's amendment.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1 and 9 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Cladaras teaches naturally occurring adenoviruses and their genomic organization. The adenoviral E3 gene encodes several different polypeptides. The mRNAs for several of these polypeptides share a common transcription initiation point and are all transcribed from the same promoter. The messages are alternatively spliced such that the 5' end of the mRNA is linked to various 3' splice sites.. Each 3' splice site is followed by different open reading frame. Each open reading frame can be considered to be a site into which a heterologous gene could be inserted. For this reason, the claims read on naturally occurring adenovirus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Cladaras et al (Virology (1/1985) 140 (1): 44-45).

Cladaras teaches naturally occurring adenoviruses and their genomic organization. The adenoviral E3 gene encodes several different polypeptides. The mRNAs for several of these polypeptides share a common transcription initiation point and are all transcribed from the same promoter. The messages are alternatively spliced such that the 5' end of the mRNA is linked to various 3' splice sites.. Each 3' splice site is followed by different open reading frame. See abstract. Each open reading frame can be considered to be a site into which a heterologous gene could be inserted.

Thus Cladaras anticipates the claims.

Claims 1, 9, 17, 18, and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Saito et al (US Patent 5,731,172, issued 3/24/98).

Saito teaches a recombinant adenoviral vector comprising a hybrid promoter, a splice acceptor site, a foreign gene, and a polyadenylation signal. The vector is used to transfect host cells and to produce a heterologous protein. See column Fig. 1. Saito is silent as to the presence of a splice donor. However, it is apparent from the disclosure that a splice donor from chicken beta actin gene is present in the construct, upstream of the rabbit beta globin splice acceptor. See column 6, lines 12-21. Saito teaches that the hybrid promoter was constructed by replacing the 3' end of an intron associated with the chicken beta actin promoter with the splice acceptor from the rabbit beta-globin gene. Thus the construct comprises a hybrid intron with a chicken beta actin intron donor site and a rabbit beta globin acceptor site. ~~See~~

Thus Saito anticipates the claims.

Claim Rejections - 35 USC § 103

Claims 1, 3, 4, 9, 17, 18, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirshenbaum et al, Quantin et al, or Stratford-Perricaudet et al, in view of Huang et al, Choi et al, Keating et al, Kabigen et al, and Saito et al (US Patent 5,731,172, issued 3/24/98).

The invention is an adenoviral expression vector comprising at least one gene insertion site, a promoter upstream of the insertion site, eukaryotic splice acceptor and done signals position downstream of the promoter and upstream of the insertion site, and a polyadenylation signal downstream of the insertion site. The promoter may be a mouse CMV early promoter. The polyadenylation signal may be the mouse beta-globin polyadenylation signal. A form of the vector containing a gene to be expressed is claimed, as is a unicellular host transformed with the vector. Methods of producing a selected protein by culturing infected or transformed hosts with the claimed vectors are also claimed.

Kirshenbaum *et al.* disclose a plasmid vector having Ad5 sequences which, when cotransfected with a mutant Ad5 construct into 293 cells, can recombine to produce a replication-incompetent virus containing the plasmid expression cassette (entire document, *e.g.* Methods). The replication cassette contains the human CMV promoter, the lacZ gene and the SV40 polyadenylation signal sequence. Kirshenbaum *et al.* also disclose transfected host cells

producing β-galactosidase. Quantin *et al.* and Stratford-Perricaudet *et al.* each disclose similar products and methods, only different promoter and polyadenylation sequences are used in the expression cassettes. None of the above three references discloses an expression cassette containing a splice site between the promoter and the gene to be expressed, nor do they disclose the use of the mouse CMV early promoter and mouse β-globin polyadenylation signal sequences. Huang *et al.* teach that including a splice site in the 5' untranslated portion of the gene to be expressed resulted in a much higher level of gene expression in several cell lines, including 293 (entire document, e.g. Fig. 2). Furthermore, Choi *et al.* (abstract) teach that incorporation of a generic intron between the promoter and the gene of interest causes 5- to 300-fold increases in transgene expression in mice. Keating *et al.* teach that the mouse immediate early CMV promoter produces a high level of gene expression in transfected cells (Table 1, Fig. 1). The KabiGen disclosure teaches that polyadenylation sequences from rodent β-globin genes yield efficient RNA processing in transfected cells (p5, lines 10-15). KabiGen also discloses vectors which contain additional cloning sites for insertion of additional genes (Figures).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the expression cassette of Kirshenbaum *et al.*, Quantin *et al.*, or Stratford-Perricaudet *et al.*, by including the splice site of either Huang *et al.* or Choi *et al.*, the murine CMV promoter of Keating *et al.*, and the murine β-globin polyadenylation sequence suggested by KabiGen. One skilled in the art would have been motivated to use these components in the expression cassette, given their recognized value for promoting high level gene expression and

given the expectation that each component would continue to function in its known and expected manner. The specific adenoviral sequence included for recombination is a result-effective variable which would have been routinely optimized by one of ordinary skill in the art.

Applicant's arguments, and the declaration of Imre Kovesdi, filed 5/30/00, and have been fully considered but they are not persuasive.

Applicant argues that one of ordinary skill in the art would not have been motivated to combine the cited references because the effect of a heterologous intron on gene expression in the context of an adenoviral vector would be so unpredictable that one could not have a reasonable expectation of success. In support of this position, Dr. Kovesdi describes the complex control of splicing in adenovirus, and indicates that one would not have considered the performance of a heterologous intron in an adenoviral vector to be predictable.

These arguments are unpersuasive in light of Saito who teaches an adenovirus expression vector comprising a hybrid CMV/enhancer/chicken beta actin promoter and splice donor, a rabbit beta actin splice acceptor, and a poly A signal. See abstract, and column 6, lines 13-21. The vector achieves effective expression in a variety of animal cells. See Fig. 1. Clearly, Saito expected the rabbit beta-actin splice acceptor to function normally in the context of the adenovirus. For this reason, one of ordinary skill in the art at the time of the invention would have been motivated to combine the references cited above, and could have done so with a reasonable expectation of success.

Thus the invention as a whole was prima facie obvious.

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kirshenbaum, Quantin, Stratford-Perricaudet, Huang, Choi, Keating, Kabigen, and Saito as applied to claims 1, 3, 4, 9, and 17-19 above, and further in view of Kitsis et al (PNAS 88: 4138-4142, 5/1991) and French et al (Circulation 90(5): 2414-2424, 11/1994).

The teachings of Kirshenbaum, Quantin, Stratford-Perricaudet, Huang, Choi, Keating, Kabigen, and Saito are summarized in the preceding rejection. Briefly, these references can be combined to render obvious an adenoviral vector comprising at least one gene insertion site, a promoter upstream of the insertion site, eukaryotic splice acceptor and done signals position downstream of the promoter and upstream of the insertion site, and a polyadenylation signal downstream of the insertion site. These references also render obvious methods of using the vector to transfect cells and produce a heterologous polypeptide encoded by a gene inserted into the vector.

These references do not teach a method of delivering the vector to an animal heart *in vivo*.

French teaches a method of delivering genes to an animal heart in vivo by use of an adenoviral vector. See abstract.

Kitsis teaches that delivery of DNA to animal heart in vivo allows the mapping of gene elements which regulate their responses to complex stimuli *in vivo*.

It would have been obvious to one of ordinary skill in the art to deliver the vector of Kirshenbaum, Quantin, Stratford-Perricaudet, Huang, Choi, Keating, Kabigen, and Saito into an animal heart in vivo. One would have been motivated to do so because Kitsis teaches that this

allows the functional analysis of constructs *in vivo*, and because Kitsis teaches that adenoviral constructs are superior to naked DNA for delivery of genes to the heart *in vivo*. One would have been motivated to use the vector of Kirshenbaum, Quantin, Stratford-Perricaudet, Huang, Choi, Keating, Kabigen, and Saito because one could reasonably expect that the presence of the intron would improve expression of the gene. See column 5, lines 18-32 of Saito, and Fig. 1.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached on Mondays and Thursdays between the hours of 6:20 AM and 3:50 PM, and on Tuesdays, Wednesdays and Fridays between the hours of 7:00 AM and 4:30 PM (Eastern time). The examiner is off every other Friday, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX phone numbers for art unit 1632 are 703-308-4242 and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Questions regarding formal matters may be directed to the Patent Analyst, Patsy Zimmerman, whose telephone number is 703-305-2758.

Richard Schnizer, Ph.D.

Karen M. Hauda

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